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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/590,421	09/08/2008	**David Ray Filpula**	213.1204-PCT-US	5480

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EXAMINER	
HISSONG, BRUCE D	
ART UNIT	**PAPER NUMBER**
1646	

NOTIFICATION DATE	DELIVERY MODE
09/07/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

info@lmiplaw.com

Office Action Summary	Application No.	Applicant(s)	
	10/590,421	FILPULA ET AL.	
	Examiner	Art Unit	
	Bruce D. Hissong, Ph.D.	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 June 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *55,57,58,61-75 and 77-109* is/are pending in the application.

4a) Of the above claim(s) *72-73 and 99-109* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *55, 57-58, 61-71, 74-75, and 77-98* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

1. Applicants' response to the office action mailed on 3/24/2010, including arguments/remarks and amended claims, was received on 6/15/2010 and has been entered into the record.

2. In the response received on 6/15/2010, the Applicants cancelled claims 56, 59-60, and 76. Claims 55, 57-58, 61-75, and 77-109 are currently pending, with claims 72-73 and 99-109 withdrawn as non-elected subject matter. Claims 55, 57-58, 61-71, 74-75, and 77-98 are presently under examination.

Claim Objections

1. Objection to claims 74, 76, and 97 regarding recitation of non-elected subject matter, as set forth on page 3 of the office action mailed on 3/24/2010, is *withdrawn* in view of Applicants' amendments to claims 74 and 97 to remove non-elected subject matter, and cancellation of claim 76.

2. Objection to claim 59 for failure for further limit the subject matter of a previous claim, as set forth on page 3 of the office action mailed on 3/24/2010, is *withdrawn* in view of Applicants' cancellation of the claim.

3. Objection to claims 68-69 for failure to further limit the subject matter of a previous claim, as set forth on page 4 of the office action mailed on 3/24/2010, is *withdrawn* in view of Applicants' amendments to the claims to depend from claim 55 rather than claim 67.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this

> subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Rejection of claims 51, 57-58, 61-71, 80-84, and 86-95 are under 35 USC § 102(e) as being anticipated by Drustrup (US 20030138403), as set forth on pages 4-5 of the office action mailed on 3/24/2010, is *withdrawn* in response to Applicants' amendments to independent claim 55 to recite a composition comprising interferon-beta-1b (IFN-β-1b).

In the response received on 6/15/2010, the Applicants argue that the compositions of the claims requires the IFN to be IFN-β-1b, and while Drustrup does mention variants of IFN-β, Drustrup points only to IFN-β-1a as preferred and is silent regarding IFN-β-1b as any part of a formulation.

These arguments have been fully considered and are persuasive.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1. Rejection of claim 85 under 35 USC § 103(a) as being obvious in view of Drustrup (US 20030138403), as set forth on page 6 of the office action mailed on 3/24/2010, is *withdrawn* in response to Applicants' arguments, discussed above, that although Drustrup discloses IFN-β formulations, it does not teach or suggest formulations comprising IFN-β-1b.

These arguments have been fully considered and are persuasive.

2. Rejection of claims 74, 77-78, and 96-98 under 35 USC § 103(a) as being obvious in view of Drustrup (US 20030138403) in view of McManus (US 20070166277), as set forth on pages 6-7 of the office action mailed on 3/24/2010, is *withdrawn* in response to Applicants' arguments, discussed above, that although Drustrup discloses IFN-β formulations, it does not teach or suggest formulations comprising IFN-β-1b, and this deficiency is not remedied by McManus.

These arguments have been fully considered and are persuasive.

3. Rejection of claims 74, 77-78, and 96-98 under 35 USC § 103(a) as being obvious in view of Drustrup (US 20030138403) in view of Saifer (US 20040126361), as set forth on page 8 of the office action mailed on 3/24/2010, is *withdrawn* in response to Applicants' arguments, discussed above, that although Drustrup discloses IFN-β formulations, it does not teach or suggest formulations comprising IFN-β-1b. Furthermore, the Applicants argue that Pepinsky *et al* (*J. Pharm. Exper. Ther.*, 2001, Vol. 297, p. 1056-1066, cited in the IDS received on 8/23/06) teaches away from formulations comprising IFN-β-1b conjugated to polyethylene glycol (PEG) because it teaches that IFN-β-1a is more potent that IFN–β-1b, and also disclosed that PEGylated IFN-β-1a PEGylated with higher molecular weight polymers had compromised activity, and thus a person of skill in the art would not have expected that the less potent IFN-b-1b would have provided good kinetics and retention of potency when PEGylated, relative to the PEGylated IFN-β-1a of Pepinsky.

These arguments have been fully considered. Although the Examiner disagrees with Applicants' contention that Pepinsky teaches away from the claimed invention, as discussed below, this rejection is withdrawn in favor of the new grounds of rejection presented below.

New Grounds of Rejection

4. Claims 55, 57-58, 61-71, and 80-95 are rejected under 35 U.S.C. 103(a) as being unpatentable over Drustrup (US 20030138403 – cited previously) in view of Durelli *et al* (*The Lancet*, 2002, Vol. 359, p. 1453-1460 – cited in the IDS received on 12/22/06).

The claims of the present invention are drawn to a composition comprising IFN-β-1b conjugated to a polyalkylene oxide polymer having a molecular weight of at least about 12 kDa, and optionally, an excipient and a buffer, wherein the pH range of the solution is from about 3 to about 5. The claims also recite the claimed composition further comprising a surfactant, such as selected from poloxyethylene sorbitol esters and polyethylene glycol. The claims also recite the IFN-β-1b composition comprising a buffer, including sodium acetate, wherein the ionic strength is about 10 mM and the buffer is in a concentration of about 3-10 mM, and wherein the composition also comprises monosaccharides, disaccharides, and alditols, and specifically mannitol. Also recited are polyalkylene oxide polymer ranges from about 12 kDa to about 60 kDa, and more specifically, 30 kDa and 40 kDa, and wherein the polyalkylene oxide polymer is conjugated to IFN-β-1b via the alpha-amino terminal of IFN-β-1b, or via an epsilon group of a lysine residue. The claims also recite a biologically-active polymer-IFN-β-1b

conjugate wherein at least about 65 percent of the antiviral activity is retained relative to native IFN-β-1b, using the EMC/Vero or EMC/A549 antiviral assay, and wherein at least about 20 percent of the antiviral activity is retained. The claims also recite method of preparing the biologically active polymer-IFN-β-1b conjugate.

Drustrup teaches a formulation comprising IFN-β conjugated to polyethylene glycol having a molecular weight of 12 kDa, wherein said formulation also comprises an acetate buffer at 10 mM, and mannitol (an excipient), wherein the pH of said formulation is 5.5 (see Example 5). Furthermore, Drustrup teaches that the IFN of the formulation can be IFN-β or a variant thereof (paragraph 0022), formulations comprising IFN at 0.1 to 10 mg/ml (paragraph 0253), teaches pH ranges from 3.0 to 8.0, and teaches use of buffers such as acetate, succinate, citrate, and glycine at various ranges, such as 1-30 mM (paragraphs 0236-0254). Drustrup also teaches incorporation of polyethylene glycol into the formulations (paragraph 0243), and also teaches various methods of conjugation/attachment of various molecular weight PEG (e.g. 5 – 100 kDa PEG – paragraph 0207) to IFN-β polypeptides, including conjugation to the amino-terminus of IFN, and conjugation to lysine residues, which would necessarily involve an amide linkage (see paragraph 0040, 0386, see also the table between paragraphs 0037 and 0038, which describes attachment of various activated PEG molecules to various regions/residues). Furthermore, Drustrup discloses specific methods of preparing conjugates comprising IFN and PEG (see Examples 3 and 5, paragraph 0384-0386). Drustrup is silent regarding a composition comprising IFN-β-1b.

However, Durelli teaches that administration of IFN-β-1b is effective in treating multiple sclerosis. Specifically, Durelli compared administration of IFN-β-1a and IFN-β-1b, and showed that a higher percentage of individuals which received IFN-β-1b remained relapse-free compared with individuals receiving IFN-β-1a (51% vs 36%, see abstract and p. 1456, 1st – 2nd columns), and a higher percentage of patients which received IFN-β-1b remained free for development of new lesions compared to patients which are received IFN-β-1a (see Figure 3 and Table 5).

Therefore, one of ordinary skill in the art, at the time the present invention was conceived, would have been motivated to create a composition comprising IFN-β-1b conjugated to a polyalkylene oxide polymer having a molecular weight of at least about 12 kDa, an excipient, a buffer solution, wherein the pH range of the solution is from about 3 to about 5, wherein said buffer solution is an acetate, citrate, succinate, or glycine buffer, and wherein the polyalkylene oxide polymer is PEG. The motivation to do so comes from the teachings of Drustrup, which teaches that IFN-β polypeptides and variants can be conjugated to 12 kDa PEG and formulated with buffers such as acetate, citrate, succinate, and glycine,

and excipients such as mannitol, and teaches or suggests various concentration ranges for the buffers and excipients. Further motivation comes from Durelli, which teaches that IFN-β-1b is effective in treating multiple sclerosis, and exhibits therapeutic properties which make use of IFN-β-1b advantageous over IFN-b-1a for said treatment of multiple sclerosis. Thus, because a skilled artisan would know that IFN-β-1b is a superior agent for treating multiple sclerosis, and Drustrup teaches formulations of IFN-β polypeptides, one of ordinary skill in the art would be motivated to substitute IFN-β-1b for the IFN-β in Drustrup.

Furthermore, in the response received on 6/15/2010, the Applicants asserted that Pepinsky *et al* teaches away from creating a composition comprising IFN-β-1b because Pepinsky teaches that IFN-β-1a is considered more potent than IFN-β-1b, and PEGylated IFN-β-1a exhibited comprised activity. It is noted, however, that the Examiner is unable to find in Pepinsky any discussion of IFN-β-1b activity relative to IFN-β-1a activity. If the Examiner is in error, then Applicants are respectfully requested to point out the specific passage(s) which contain this teaching. However, even if IFN-β-1b exhibited decreased activity relative to IFN-β-1a, Durelli teaches that IFN-β-1b is superior to IFN-β-1a for treatment of multiple sclerosis, as discussed above. Regarding Applicants assertion that Pepinsky teaches away from the present invention by showing that PEGylated IFN-β-1a performed poorly due to comprised activity, it is noted that the section of Pepinsky quoted by the Applicants seems to be restricted to *in vitro* activity of IFN-β-1a, and does not teach or suggest anything regarding the *in vivo* pharmaceutical properties of PEGylated IFN-β-1b.

Finally, regarding the limitations that the claimed conjugate retain at least about 65 percent, or at least about 20 percent of the antiviral activity relative to native IFN-β-1b using the EMC/Vero or EMC/A549 antiviral assays, it is noted that while neither Drustrup nor Durelli specifically teach these limitations, the formulations and methods of conjugation disclosed by Drustrup are the same as those presently claimed, and in absence of evidence to the contrary, an IFN-β-1b formulation produced by the methods of conjugation of Drustrup would be expected to exhibit these activities. Because the USPTO does not have the facilities for testing the conjugates/formulations of Drustrup, the burden is on the Applicants to show a novel and unobvious difference between the claimed compositions/conjugates and those of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

5. Claims 74, 77-79, and 96-98 are rejected under 35 U.S.C. 103(a) as being unpatentable over Drustrup (US 20030138403) in view of Durelli *et al* (*The Lancet*, 2002, Vol. 359, p. 1453-1460 – cited in the IDS received on 12/22/06), and further in view of McManus *et al* (US 20070166277 - cited previously).

Claims 74, 77-69, and 96-98 are drawn to the claimed composition comprising IFN-b-1b conjugated to a polyalkylene oxide of at least 12 kDa, wherein the polyalkylene oxide polymer is the elected polymer depicted on page 14 of the Applicants' response of 11/23/2009, wherein the molecular weight of the polyalkylene oxide polymer ranges from about 12 kDa to about 60 kDa, and specifically 30 kDa or 40 kDa. The claims also recite a conjugate comprising an activated polyethylene glycol with an $mPEG_2CH_2CH_2CH_2CHO$ structure, and methods of preparing an IFN conjugate comprising the elected polyalkylene oxide shown on page 14 of the 11/23/09 response, and wherein the activated polyethylene glycol comprises the elected terminal reactive moiety shown on page 16 of the 11/23/09 response.

The disclosures of Drustrup and Durelli are discussed above. Both are silent regarding conjugation of IFN-β to the polyalkylene oxide polymer shown on page 14 of the 11/23/09 response, or comprising the terminal reactive moiety shown on page 16 of the same response. However, McManus teaches a 40 kDa succimidyl ester of PEG_2 which is identical to the elected polyalkylene oxide polymer shown on page 14 of the 11/23/09 response, wherein this polymer also comprises the elected terminal reactive moiety, and has the overall structure shown on page 16 of the 11/23/09 response (see Example 6 of McManus). McManus teaches the use of this succimidyl PEG2 ester for the use of conjugating PEG to various polypeptides, including IFN-β (see Example 15). McManus also teaches polymeric agents with a $CH_2CH_2CH_2CHO$ spacer structure separating the polymer, such as PEG, and the biological protein (paragraph 0172).

Therefore, it would have been obvious to one of ordinary skill in the art, at the time the present invention was conceived, to prepare a conjugate comprising IFN-β-1b conjugated to a polyalkylene oxide polymer of at least 12 kDa, wherein the polyalkylene oxide polymer is the polymer elected by Applicants and shown on page 14 of the 11/23/09 response, and wherein this polymer also comprises the terminal reactive moiety shown on page 16 of the 11/23/09 response. The motivation to do so comes from the disclosure of Drustrup and Durelli, which as discussed above provide the motivation to create compositions comprising IFN-β-1b, wherein the IFN-β-1b is conjugated to a polyalkylene oxide polymer (PEG) that is 12 kDa (Example 5), and also teaches conjugation to PEG molecules having a molecular weight between 10 kDa and 40 kDa (paragraph 0070). Further motivation comes from McManus, which discloses a polyalkylene oxide moiety with the same structure as the elected polyalkylene oxide shown on

page 14 of the 11/23/09, and also comprising the terminal reactive moiety shown on page 16 of the 11/23/09 response, and conjugation of this polyalkylene oxide moiety to polypeptides such as IFN-β. Therefore, because Drustrup and Durelli suggest a composition comprising an IFN-b-1b polypeptide conjugated of to polyalkylene oxide polymers having a molecular weight of at least 12 kDa, and McManus teaches a specific polyalkylene oxide polymer that is identical to Applicants' elected polymer, and the use of this polymer for conjugation to polypeptides such as IFN-β, it would have been obvious to one of ordinary skill in the art to conjugate the succimidyl PEG ester of McManus to IFN-β and create a composition comprising acetate buffer, mannitol, PEG as a stabilizer/surfactant, and at the pH ranges taught by Drustrup.

6. Claim 75 is rejected under 35 U.S.C. 103(a) as being unpatentable over Drustrup (US 20030138403) in view of Durelli *et al* (*The Lancet*, 2002, Vol. 359, p. 1453-1460 – cited in the IDS received on 12/22/06), and further in view of Saifer *et al* (US 20040126361 - cited previously).

Claim 75 is drawn to the composition of claim 55, wherein the IFN-β-1b comprises the amino acid sequence of SEQ ID NO: 1. The disclosures of Drustrup and Durelli are discussed above. Although Drustrup clearly contemplates formulations comprising an IFN conjugated to PEG, wherein the IFN is IFN-α, IFN-β, or variants thereof (paragraph 0022), of which IFN-β-1b would be an art-recognized variant of IFN-β, Drustrup does not explicitly teach an IFN polypeptide comprising the sequence of SEQ ID NO: 1. Furthermore, although Durelli teach treatment of multiple sclerosis with pharmaceutical compositions comprising IFN-b-1b, Durelli does not explicitly teach SEQ ID NO: 1)

However, Saifer teaches an IFN-β-1b polypeptide which is identical to the amino acid sequence of SEQ ID NO: 1 (see sequence comparison in the office action mailed on 3/24/2010). Saifer also teaches conjugation of this polypeptide to PEG (see Example 4), and teaches that pharmaceutical compositions comprising IFN-β are useful for treating IFN-β-responsive disorders, including certain cancers, infectious disease, autoimmune disorders (see claims 25, 50, 55-58).

Therefore, one of ordinary skill in the art, at the time the present invention was conceived, would have been motivated to create a formulation comprising the IFN-β-1b polypeptide of SEQ ID NO: 1, wherein this IFN-β-1b polypeptide was conjugated to a polyalkylene oxide polymer of at least 12 kDa, and wherein said formulation also comprised an excipient and a buffer, wherein the pH range of the solution is from about 3 to about 5. The motivation to do so comes from the combined teachings of Durelli and Saifer, which disclose a IFN-β-1b polypeptide which is identical to SEQ ID NO: 1 of the instant application and which can be conjugated to PEG (Saifer) and which is therapeutically useful

(Durelli), and a formulation for such IFN-β polypeptides comprising an excipient, a buffer, and wherein the pH range of the solution is from about 3 to about 5 (Drustrup). Thus, one of ordinary skill in the art, knowing that the formulation of Drustrup is an effective formulation for therapeutic IFN-β polypeptides, would be motivation to formulate the IFN-β-1b of Saifer by the methods of Drustrup to create an effective therapeutic formulation of IFN-β-1b useful for treatment of multiple sclerosis, as suggested by Durelli.

Conclusion

No claim is allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bruce D. Hissong, Ph.D., whose telephone number is (571)272-3324. The examiner can normally be reached M-F from 8:30 am - 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, Ph.D., can be reached on (571) 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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/Robert Landsman/
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